AR201-126676$_3$

IRGAFOS 168

Tris(2,4-di-(tert)-butylphenyl)phosphite

CAS No. 31570-04-4

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Name of Sponsoring Organization:	Ciba Specialty Chemicals Corporation
HPV Registration Number:	
Technical Contact Persons:	Richard Balcomb and David La
Address:	Additives Legal and Regulatory Affairs
Street:	540 White Plains Road
Town:	Tarrytown
State:	New York
Postal code:	10591
Country:	US
Tel:	(914) 785-2000
Fax:	(914) 785-4147

May 2000

MR36601

CONTENTS

1. MELTING POINT

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 31570-04-4
Method:	Estimated by the MPBPWIN Program (v. 1.40)[1] using the adapted Joback method and the Gold and Ogle method.
GLP:	No
Year:	2000
Results:	268.5 °C
Remarks:	The melting point calculation by an accepted method is assigned a reliability code of 2f.[2]
References:	[1]Syracuse Research Corporation, Syracuse, NY Pollution Prevention (P2) Assessment Framework, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (Draft), 1998 [2]See general reference, p. 37.

2. BOILING POINT

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 31570-04-4
Method:	Estimated by the MPBPWIN Program (v. 1.40)[1] using the adapted Stein and Brown method.
GLP:	No
Year:	2000
Results:	619.8 °C
Remarks:	The boiling point calculation by an accepted method is assigned a reliability code of 2f.
References:	[1]Syracuse Research Corporation, Syracuse, NY Pollution Prevention (P2) Assessment Framework, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (Draft), 1998

3. VAPOR PRESSURE

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 31570-04-4
Method:	Estimated by the MPBPWIN Program (v. 1.40)[1] using the modified Grain method.
GLP:	No
Year:	2000
Results:	4.7×10^{-14} mm Hg
Remarks:	The vapor pressure calculation by an accepted method is assigned a reliability code of 2f.
References:	[1]Syracuse Research Corporation, Syracuse, NY Pollution Prevention (P2) Assessment Framework, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (Draft), 1998

4. PARTITION COEFFICIENT

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 31570-04-4
Method:	Estimated by the KOWWIN Program (v. 1.66).[1]
GLP:	No
Results:	Log P = 18.1
Remarks:	The partition coefficient calculation by an accepted method is assigned a reliability code of 2f.
References:	[1]Syracuse Research Corporation, Syracuse, NY Pollution Prevention (P2) Assessment Framework, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (Draft), 1998

5. WATER SOLUBILITY

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 31570-04-4
Method:	Estimated by the WSKOW Program (v. 1.37).[1]
GLP:	No
Results:	The chemical is predicted to be insoluble Solubility at 25 °C = 2.9 x 10^{-14} mg/L
Remarks:	The water solubility calculation by an accepted method is assigned a reliability code of 2f.
References:	[1]Syracuse Research Corporation, Syracuse, NY Pollution Prevention (P2) Assessment Framework, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (Draft), 1998

6. PHOTODEGRADATION

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 31570-04-4
Method:	Estimated by the AOP program (v. 1.90),[1] which estimates rate constants and half-lives of atmospheric reactions of organic compounds with hydroxyl radicals and ozone in the atmosphere.
GLP:	No
Results:	For reaction with hydroxyl radicals, the predicted half-life of the chemical is moderate. Rate constant: 23.9×10^{-12} cm^3/molecule-sec Half-life: 5.4 h
Remarks:	The photodegradation calculation by an accepted method is assigned a reliability code of 2f.
References:	[1]Syracuse Research Corporation, Syracuse, NY Pollution Prevention (P2) Assessment Framework, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (Draft), 1998

7. STABILITY IN WATER

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 31570-04-4
Method:	Evaluated by the HYDROWIN Program (v. 1.67).
GLP:	No
Year:	2000
Results:	The program was unable to evaluate this chemical structure.
References:	[1]Syracuse Research Corporation, Syracuse, NY Pollution Prevention (P2) Assessment Framework, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (Draft), 1998

8. THEORETICAL DISTRIBUTION (FUGACITY CALCULATION)

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 31570-04-4
Method:	Estimated by Level III Fugacity Model.[1]
Year:	2000
GLP:	No
Results:	Distribution using Level III Fugacity Model

Air	0.053%
Water	1.19%
Soil	36.1%
Sediment	62.6%

Remarks: The fugacity calculation by an acceptable method is assigned a reliability code of 2f.

References: [1]Syracuse Research Corporation, Syracuse, NY

9. BIODEGRADATION

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 31570-04-4 Batch No. EN 128985.82
Method:	OECD Guideline No. 301B (Paris 1981). Bacteria was collected from activated sludge of a sewage treatment plant. The preparation was carried out according to the method described in the guideline. The volume of the test solution was reduced from 3 l to 1.5 l. The CO_2 formed by biodegradation was absorbed with NaOH and determined on a carbon analyzer. Due to the poor solubility of the test substance in water, an emulsifier was used to achieve a better distribution in the medium. The test substance was added to the medium and homogenized with Nonylphenol 10EO5PO.
Test Type:	Aerobic
Inoculum:	Fresh sewage treatment plant sample (per guideline).
Concentration of the chemical:	11.4 mg/L 21.5 mg/L
Medium:	Sewage sludge (per guideline)
GLP:	No
Year:	1989
Results:	11.4 mg test substance/L = 6% in 28 days 21.5 mg test substance/L = 3% in 28 days
Conclusion:	This chemical was not biodegradable in this test.
Remarks:	This study is assigned a reliability code of 2a, as it was conducted under OECD, but not GLP guidelines.
Reference:	Report on the test for ready biodegradability of TK 11682 in the modified Sturm test. Project No. 88 45 80, Ciba-Geigy Ltd., Basel Switzerland, 1989.

10. ACUTE TOXICITY TO FISH

Test substance: Tris(2,4-di-(tert)-butylphenyl)phosphite
CAS No. 31570-04-4

Method: Test was based on the method reported by Bathe *et al* (1974). Fish were placed in 12 L tanks containing reconstituted water prepared as described by Bathe *et al* (1974). Four fish were placed per tank. The test material was dissolved in acetone and added to the tanks. The tanks were maintained at 14 $\pm$ 2 °C. Dissolved oxygen and pH were monitored at 24 h intervals throughout the 96 h testing period.

Species: Bluegill (Lepomis macrochirus)

Exposure period: 96 h

GLP: No

Year: 1976

Results: LC_{50} = 84 ppm

Remarks: This study was not conducted under OECD or GLP guidelines. The study is assigned a reliability code of 2e (meets generally accepted scientific standards, is well documented, and is acceptable for assessment). Several other species also were tested in this study, and these results are summarized below:

Species	LC50 (96 h)
Rainbow trout (Salmo gairdneri)	49 ppm
Carp (Cyprinus carpio)	66 ppm
Catfish (Ictalurus melas)	70 ppm
Golden orfe (Leuciscus idus forma orfus	42 ppm

The test material had slight acute toxicity to trout and golden orfe, and was practically devoid of acute toxicity to carp, catfish, and bluegill.

References: "Acute toxicity to rainbow trout, carp, catfish, bluegill and golden orfe of TK 11682." Siss 5496, Ciba-Geigy Ltd, Basel, Switzerland, 1976.

Bathe, R., Sachsse, K., Ullmann, L., Hormann, W.D., Zak, F., and Hess, R., "The evaluation of fish toxicity in the laboratory." In Proceedings of the European Society of Toxicology, Vol XVI, pp. 113-124, 1974.

11. TOXICITY TO AQUATIC PLANTS

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 31570-04-4 Batch No. N 26824
Method:	87/302/EEC page 89-94 Algal growth inhibition test. Determination of EbC 50: concentration which reduced the growth of algae 50% relative to control. The test compound was dissolved in a solution containing TWEEN80 to enhance solubility.
Species:	Green Algae (Scenedesmus subspicatus)
Test concentrations (actual):	1.1, 3.1, 8.1, 23.8, 75.2 mg/L
Exposure period:	72 h
Analytical monitoring:	Yes
GLP:	Yes
Year:	1993
Results:	EbC_{50} (0-72 h) > 75.2 mg/L NOEbC (0-72 h) = 75.2 mg/L
Remarks:	This study is assigned a reliability code of 1 (reliable without restrictions) according to the criteria established by Klimisch *et al* (1997).
Reference:	"Report on the growth inhibition test of IRGAFOS 168 to Green Algae (Scenedesmus subspicatus)." Test No. 928138, Ciba-Geigy Limited, Basel, Switzerland, 1993.

12. ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 31570-04-4 Batch No. EN 128985.82
Method:	OECD Guideline No. 202, Part I, 1984. Determination of EC50 (24 h), the concentration at which 50% of the daphnia population is immobilized.
Type of test:	Static
Species:	Daphnia magna Straus 1820
No. animals:	20 daphnia/concentration and control (4 replicates of 5 daphnia each)
Exposure period:	24 h
Analytical monitoring:	No
GLP:	No
Year:	1988
Results:	EC_{50} (24 h) calculated = 510 mg/L EC_0 (24 h) = 180 mg/L EC_{100} (24 h) = 1000 mg/L
Remarks:	This study is assigned a reliability code of 2a, as it was conducted under OECD, but not GLP guidelines.
Reference:	"Test for acute toxicity of TK 11682 to Daphnia magna." Project No. 884581. Ciba-Geigy Limited, Basel, Switzerland, 1988.

13. ACUTE TOXICITY

A. ORAL

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 31570-04-4
Method:	The test substance was suspended in polyethylene glycol (PEG 400), dispersed, and administered to rats by gavage. Following single exposure, animals were observed for up to 7 additional days.
Species/strain:	Rat [Tif:RAI]
Sex:	20 Male; 20 Female
No. Animals/Group:	5 Male and 5 female rats/group
Doses:	1000, 3170, 4640, 6000 mg/kg in PEG 400
Post dosing observation period:	7 days
GLP:	No
Year:	1974
Results:	LD_{50} > 6000 mg/kg[1] Within 2 h after exposure, the rats exhibited sedation, dyspnoea, exophthalmus, curved position, and ruffled fur. Animals recovered within 6 to 7 days. No deaths occurred during the study.
Remarks:	This study was not conducted under OECD or GLP guidelines. The study is assigned a reliability code of 2e (meets generally accepted scientific standards, is well documented, and is acceptable for assessment). The results were consistent with two other studies that reported an acute oral LD_{50} > 6000 mg/kg in the mouse,[2] and > 6000 mg/kg in the Chinese hamster.[3]
References:	[1]"Acute oral LD50 of TK-11682 in the rat." Project No. Siss 3863, Ciba-Geigy Limited, Basel, Switzerland, 1974. [2]"Acute oral LD50 in the mouse of TK 11682." Project No. Siss 6236, Ciba-Geigy Limited, Basel, Switzerland, 1977a. [3]"Acute oral LD50 in the Chinese hamster [Cricetulus griseus] of TK 11682." Siss 6236, Ciba-Giegy Limited, Basel, Switzerland, 1977b.

B. DERMAL

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 31570-04-4 Batch No. N 26824
Method:	OECD 402, "Acute Dermal Toxicity," adopted February 24, 1987. 10 Rats (5 male and 5 female) were treated with a single dose (2000 mg/kg) of the test material applied to the skin. Material was applied to 10% of the body surface for 24 h. Animals were observed for 14 days post-exposure.
Species/strain:	Rat [Tif:RAI f(SPF)]
No. Animals	10 (5 Male/5 Female)
Dose:	2000 mg/kg
Vehicle:	0.5% (w/v) carboxymethylcellulose in 0.1% (w/v) aqueous polysorbate 80.
Exposure period:	24 h
Post-exposure observation:	14 days
GLP:	Yes
Year:	1992
Results:	LD_{50} > 2000 mg/kg body weight Piloerection and hunched posture were common symptoms. These animals recovered within 2 days. No mortalities occurred in this study.
Remarks:	This study is assigned a reliability code of 1 (reliable without restrictions) according to the criteria established by Klimisch *et al* (1997).
Reference:	Acute dermal toxicity in the rat, Test No. 924065, TK 11582 (Irgafos 168), Ciba-Geigy Limited, Basel, Switzerland, 1992.

14. GENETIC TOXICITY IN VIVO

A. SISTER CHROMATID EXCHANGE

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 31570-04-4 Batch No. EN 008/77
Method:	Chinese hamsters were administered the test compound by gavage, and sacrificed 24 h after the exposure and 2 h after an i.p. injection of colcemide. From the bone marrow, drop-preparations were made and stained according to a modified fluorochrome plus Giemsa technique (Perry and Wolf, 1974; Goto *et al*, 1978; Allen *et al*, 1977). Slides were scored for the number of sister chromatid exchanges (Perry and Evans, 1975).
Type:	Sister chromatid exchange
Species/strain:	Chinese hamster
Sex:	4-6 Males/4-6 Females per group
Route of Administration:	Gavage
Exposure period:	Single exposure
Doses:	1111, 2222, 4444 mg/kg (original study) 1777, 2666, 4000, 6000 mg/kg (follow-up study)
GLP:	No
Year:	1982, 1989
Results:	There was no evidence of treatment effect on sister chromatid exchange. This study was originally conducted in 1982 during which slides from 3 animals/sex/dose were analyzed. In this supplemental study, additional slides were scored, to extend the analysis to 5 animals/sex/dose. Based on this supplemental analysis, the number of sister chromatid exchanges per cell in animals treated with the 6000 mg/kg showed a small, but significant increase compared to control. However, the 6000 mg/kg dose exceeds the maximum recommended dose of 2000 to 5000 mg/kg, and this finding was interpreted as biologically not relevant.
Remarks:	This study was not conducted under formal test guidelines. The study is assigned a reliability code of 2e, as it meets generally accepted

scientific standards, is well documented, and is acceptable for assessment. The findings are consistent with a study of chromosomal aberrations, in which Chinese hamsters were administered the test compound (500, 1000, or 2000 mg/kg) daily for 2 days. Analysis of cells from bone marrow did not reveal chromatid or chromosome-type aberrations (Ciba-Geigy, 1980).

References:

"Sister chromatid exchange study, TK 11 682, Chinese hamster." Experiment No. 800586, Ciba-Geigy Limited, Basel, Switzerland, 1982.

"Sister chromatid exchange study, Chinese hamster." Test No. 800586, Ciba-Geigy Limited, Basel, Switzerland, 1989.

"Chromosome studies in somatic cells, TK 11 682, Chinese hamster." Experiment No. 783106, Ciba-Geigy Limited, Basel, Switzerland, 1980.

Perry, P. and Wolff, S., New Giemsa method of the differential staining of sister chromatids, Nature, 251, 156-158, 1974.

Goto, K., Maeda, S., Kano, Y., and Sugiyama, T., Factors involved in differential Giemsa-staining of sister chromatids, Chromosoma, 66, 351-359, 1978.

Allen, J.W., Shuler, C.F., Mendes, R.W., and Latt, S.A., A simplified technique for in vivo analysis of sister chromatid exchanges using 5-bromodeoxyuridine tablets, Cytogenet. Cell Genet., 18, 231-237, 1977.

Perry, P. and Evans, H.J., Cytological detection of mutagen-carcinogen exposure by sister chromatid exchange, Nature, 258, 121-125, 1975.

B. CHROMOSOMAL ABERRATIONS

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 31570-04-4
Method:	The test compound was administered by gavage over a period of 10 days on days 0, 2, 3, 5, and 9. Three days after the final dose and 3 h after an *i.p.* injection of colcemide, animals were killed, and drop-preparations were made of testicular parenchyma. Primary and secondary spermatocytes were assessed for chromosomal aberrations.
Type:	Chromosome studies of spermatocytes
Species/strain:	Mouse (NMRI-derived strain)
Sex:	Male, 15/group
Route of Administration:	Gavage
Exposure period:	Days 0, 2, 3, 5, 9
Doses:	1481, 4444 mg/kg (in 20 mL/kg polyethylene glycol
Control:	Concurrent, 20 mL/kg polyethylene glycol
GLP:	No
Year:	1982, 1989
Results:	No evidence of mutagenic activity of the test compound, as indicated by chromosomal aberrations.[1,2]
Remarks:	This study was not conducted under formal test guidelines. The study is assigned a reliability code of 2e, as it meets generally accepted scientific standards, is well documented, and is acceptable for assessment. The findings are consistent with a study assessing chromosomal aberrations in spermatogonia.[3,4] In that study, male mice were administered the test compound (1481 or 4444 mg/kg) daily for 5 consecutive days. Chromosomal analysis of spermatogonia did not reveal increased aberrations.
References:	[1]"Chromosome studies in male germinal epithelium TK 11 682, mouse, test for mutagenic effects on spermatocytes." Experiment No. 782928, Ciba-Geigy Limited, Basel, Switzerland, 1982.

[2]"Chromosome studies in male germinal epithelium, mouse, test for mutagenic effects on spermatocytes." Test No. 782928, Ciba-Geigy Limited, Basel, Switzerland, 1989.

[3]"Chromosome studies in male germinal epithelium, TK 11 682, mouse, test for mutagenic effects on spermatogonia." Experiment No. 782927, Ciba-Geigy Limited, Basel, Switzerland, 1982.

[4]"Chromosome studies in male germinal epithelium, mouse, test for mutagenic effects on spermatogonia." Test No. 782927, Ciba-Geigy Limited, Basel, Switzerland, 1989.

C. NUCLEUS ANOMALY

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 31570-04-4
Method:	The test compound was administered by gavage daily for 2 consecutive days. Animals were sacrificed 24 h after the second administration, and bone marrow smears were made. Slides (1000 bone marrow cells) were scored for the following anomalies: single Jolly bodies, fragments of nuclei in erythrocytes, micronuclei in erythroblasts, micronuclei in leucopoietic cells, and polyploid cells.
Type:	Nucleus anomaly test in somatic interphase nuclei
Species/strain:	Chinese hamster
Sex:	6 Males/6 Females/group
Route of Administration:	Gavage
Exposure period:	2 Days
Doses:	500, 1000, 2000 mg/kg/day
GLP:	No
Year:	1980
Results:	The incidence of bone marrow cells with anomalies of nuclei was not significantly different between treatment and control groups.
Remarks:	This study was not conducted under formal test guidelines. The study is assigned a reliability code of 2e, as it meets generally accepted scientific standards, is well documented, and is acceptable for assessment.
Reference:	"Nucleus anomaly test in somatic interphase nuclei, TK 11 682, Chinese hamster." Experiment No. 78-3006, Ciba-Geigy Limited, Basel, Switzerland, 1980.

D. DOMINANT LETHAL

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 31570-04-4
Method:	Male mice were administered a single dose of the test material by gavage, and mated for 6 weeks with untreated female mice. The females and progeny were examined
Type:	Dominant lethal
Species/strain:	Mouse, NMRI-derived (Tif:MAG f[SPF])
Sex:	Male, 20/group
Route of Administration:	Gavage
Exposure period:	Single exposure
Doses:	1000, 3000 mg/kg
GLP:	No
Year:	1978
Results:	There was no evidence of dominant lethal effects or reduced male fertility.
Remarks:	This study was not conducted under formal test guidelines. The study is assigned a reliability code of 2e, as it meets generally accepted scientific standards, is well documented, and is acceptable for assessment.
Reference:	"Dominant lethal study - TK11682 (Irgafos 168)." Project No. 784820, Ciba-Geigy Limited, Basel, Switzerland, 1978.

15. GENETIC TOXICITY IN VITRO

A. Mutagenic Effects in Bacteria

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 31570-04-4
Method:	This study was not conducted under OECD guidelines, but was conducted using the methods described by Ames *et al* (1973, 1973, 1975). The material was tested for mutagenic effects on histidine auxotrophic mutants of Salmonella typhimurium. Cultures were prepared from frozen stock, and on the following day the standard plate test was carried out. The concentrations of the test substance were 0, 1, 3, 9, 27, 81 µg/0.1 mL. In the experiments in which the substance was metabolically activated, 0.5 mL of the activation mixture (S9 fraction of liver from rats induced with Arochlor 1254 plus co-factors) was added. Positive controls in the form of spot tests were also included. After incubation for 48 h, plates were analyzed for revertants.
Type:	Reverse mutation
System of testing:	Salmonella typhimurium TA 98, 100, 1535, 1537
Concentration:	0, 1, 3, 9, 27, 81 µg/0.1 mL
Metabolic activation:	With and without S9 liver fraction from rats induced with Arochlor 1254.
GLP:	No
Year:	1978
Results	No increase in mutations with or without metabolic activation.
Remarks:	This study was not conducted under formal guidelines. However, the study meets generally accepted scientific standards, is well documented, and is acceptable for assessment (reliability code 2e).
References:	"Salmonella/mammalian-microsome mutagenicity test with TK 11682." Experiment No. 78-2515, Ciba-Geigy Limited., Basel, Switzerland, 1978. Ames, B.N., Lee, F.D., and Durston, W.E., "An improved bacterial test system for the detection and classification of mutagens and carcinogens, Proc. Natl. Acad. Sci. USA, 70, 782-786, 1973.

Ames, B.N., Durston, W.E., Yamasaki, E., and Lee, F.D., "Carcinogens are mutagens: a simple test system combining liver homogenates for activation and bacteria for detection," Proc. Natl. Acad. Sci. USA, 70, 2281-2285, 1973.

Ames, B.N., McCann, J., and Yamasaki, E., "Methods for detecting carcinogens and mutagens with the Salmonella/mammalian-microsome mutagenicity test, Mutat. Res., 31, 347-364, 1975.

B. Mutagenic Effects in Yeast Cells

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 31570-04-4
Method:	Yeast cells in culture were centrifuged and resuspended in water to a density of 1 to 5 x 10^8 cells/mL. The suspension (9 mL) was transferred to test bottles containing 1 mL of the test substance dissolved in DMSO. Following incubation for 3.5 h at 25 °C, the yeast cells were plated to determine the number of surviving cells and mutants.
System of testing:	Saccharomyces cerevisiae MP-1
Concentration:	625, 1250, 2500, 5000, 10000 µg/mL
Metabolic activation:	No
GLP:	No
Year:	1982
Results	Not mutagenic
Remarks:	This study was not conducted under formal guidelines. However, the study met generally accepted scientific standards, was well documented, and was acceptable for assessment (reliability code 2e).
Reference:	"Mutagenicity test on Saccharomyces cerevisiae MP-1 in vitro with TK 11 682." Experiment No. 820052, Ciba-Geigy Limited, Basel, Switzerland, 1982.

16. REPEATED DOSE TOXICITY

A. 28-Day Gavage Study in Rats

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 31570-04-4
Method:	60 Rats (5 male and 5 female/group) were administered the test substance by gavage daily for 28 days. During the exposure period, animals were examined daily for clinical symptoms and body weight and weekly for food consumption. Ophthalmic examinations were performed pre-test and at week 4. Following final treatment, animals were sacrificed, and organs and tissues were examined macroscopically and microscopically. Additional rats (10 controls and 10 high dose group) were observed for 28 days post-exposure, and examined similarly at sacrifice.
Species/strain:	Sprague Dawley rat
No. animals/group:	5 Male and 5 Female/group
Route of administration:	Gavage
Exposure period:	28 Days
Frequency of treatment:	Daily
Post exposure observation period:	28 Days
Dose:	10, 50, or 250 mg/kg
Vehicle:	2% carboxymethyl cellulose
Control group:	Yes, concurrent vehicle
GLP:	No
Year:	1975
Results:	NOEL = 250 mg/kg/day No abnormal clinical symptoms were observed, and no animals died during the study. The test chemical did not significantly affect body weight or laboratory parameters (hematology and clinical chemistry). No effects of the test chemical were observed during necropsy or on histopathological examination.

Remarks:	This study was not conducted under formal guidelines. However, the study met generally accepted scientific standards, was well documented, and was acceptable for assessment (reliability code 2e).
Reference:	"28 Day oral toxicity study in rats with compound TK 11 682." Project No. 7DO3, Geigy Pharmaceuticals, Stamford Lodge, UK, 1975.

B. 90-Day Gavage Study in Rats

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 31570-04-4
Method:	220 Rats were assigned to one of five treatment groups, and were exposed to the test chemical by gavage daily for 13 weeks. During the exposure period, animals were examined daily for clinical symptoms and weekly for body weight and food consumption. For control and high-dose group animals, urinalysis was conducted during weeks 4, 12, and 17, hematology during weeks 0, 4, 12, and 17, blood chemistry during weeks 4, 12, and 17, and ophthalmic examinations were during weeks 0, 6, 13, and 17. Following final treatment, animals were sacrificed, and organs and tissues were examined macroscopically and microscopically. Additional rats (10 controls and 10 high-dose group) were observed for 4 weeks post exposure, and examined similarly at sacrifice.
Species/strain:	Sprague Dawley rat
No. animals/group:	20 Male and 20 Female rats/dose group
Route of administration:	Gavage
Exposure period:	13 Weeks
Frequency of treatment:	Daily
Post exposure observation period:	4 Weeks
Dose:	125, 250, 500, 1000 mg/kg/day
Control group:	Concurrent vehicle (1% caboxymethyl cellulose)
GLP:	No
Year:	1976
Results:	NOEL = 500 mg/kg/day No relevant clinical symptoms and no signs of systemic toxicity were observed during the study. The eye examinations and urine analysis revealed no deviations from controls. The body weight gain and the absolute and relative organ weights were within the control ranges, with the exception of the females from the high dose group, which had higher kidney weights at the end of the treatment and the recovery period. The increased kidney weights were not associated with

histopathological changes, and were unlikely to be of toxicological significance.

Remarks: This study was not conducted under formal test guidelines, but does meet generally accepted scientific standards, is well documented, and is acceptable for assessment (reliability code 2e).

Reference: "TK 11 682 Toxicity to rats, repeated oral administration for 13 weeks." Project No. CGB167/76339, Huntingdon Research Centre, Huntingdon, UK, 1976.

C. 90-Day Feeding Study in Dogs

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 31570-04-4
Method:	32 Dogs (16 male/16 female) were divided into one of four groups, and were fed the test compound (0, 719, 2208, or 8092 ppm) daily for 3 months. Additional animals (2 control and 2 high-dose group) were included to study recovery. Animals were examined daily for clinical symptoms, and food/water intake and weekly for body weight. Ophthalmic and hearing examinations were performed pretest and during weeks 4, 8, and 13 (and week 17 for recovery animals). Blood samples for hematology and clinical chemistry and urine samples were collected pretest and during weeks 4, 9, and 13 (and week 17 for recovery animals). During necropsy, organs and tissues were examined macroscopically and microscopically.
Species/strain:	Beagle dogs
No. animals/group:	4 Male and 4 Female/dose group
Route of administration:	Dietary
Exposure period:	3 Months
Frequency of treatment:	Daily
Post exposure observation period:	28 Days
Dose:	0, 1000, 3000, 10000 ppm (nominal) 0, 719, 2208, 8092 ppm (actual)
Control group:	Concurrent, control diet
GLP:	No
Year:	1978
Results:	NOEL > 318 mg/kg/day No abnormal clinical symptoms were observed, and no animals died during the study. Food and water consumption in all groups were similar. No effects were noted during eye and hearing tests. The test chemical did not significantly affect body weight or laboratory parameters (hematology, clinical chemistry, urinalysis). No effects of the test chemical were observed during necropsy or on histopathological

examination. The NOEL was determined to be > 8092 ppm, which corresponds to 318 mg/kg/day.

Remarks: This study was not conducted under formal test guidelines, but does meet generally accepted scientific standards, is well documented, and is acceptable for assessment (reliability code 2e).

Reference: "3 Month dietary toxicity study in dogs with compound TK 11 682." Project No. 7DO3, Geigy Pharmaceuticals, Stamford Lodge, UK, 1978.

17. REPRODUCTIVE TOXICITY

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 31570-04-4 Batch No. EN 47503.22
Method:	Diets containing 0, 1600, 4000, or 10,000 ppm of the test material were fed continuously over the period of 18 weeks to parent F0 and F1. The periods of exposure included 12-day mating periods for each parental generation. The F1 rats were additionally exposed to the test substance in utero and during lactation. Likewise, the F2 generation was exposed to the test substance from embryogenesis through weaning. The F0 and F1 parent rats were sacrificed after weaning of the F1 and F2 sucklings, respectively. Histopathological examination of organs was performed on all adults from the control and 10,000 ppm groups and a selected number of each of the F1 and F2 weanlings from these groups. For rats in the low and intermediate dose groups the tissues were retained for future reference.
Type:	Two-generation reproduction toxicity study
Species/strain:	Rat [Tif:RAI f(SPF)]
Sex:	Male/Female
Route of Administration:	Dietary
Exposure period:	18 weeks
Frequency of treatment:	Daily
Doses:	0, 1600, 4000, 10000 ppm
Control group:	Concurrent, standard diet
GLP:	Yes
Year:	1985
Results:	The test compound was slightly toxicity to the F0 females exposed to 10,000 ppm, as exhibited by a transient reduction in body weight. In animals from the other groups, no differences in body weight were observed. There were no clinical or systemic effects attributed to treatment, and there were no macro or histopathological findings that were related to the treatment. The F1 adults, F1 pups and F2 pups exosed to 10,000 ppm did not reveal adverse reactions to the treatment.

Remarks:	This study is assigned a reliability code of 1d (meets generally accepted scientific standards and is described in sufficient detail) according to the criteria established by Klimisch *et al* (1997).
Reference:	"Report on Irgafos 168 (TK 11 682), Two-generation reproduction toxicity study in rats." Test No. 82 0873, Ciba-Geigy Ltd., 1985.

18. DEVELOPMENTAL TOXICITY/ TERATOGENICITY

Test substance:	Tris(2,4-di-(tert)-butylphenyl)phosphite CAS No. 31570-04-4 Batch No. EN 46776.12
Method:	OECD Guideline No. 414 (Teratogenicity). The test chemical was suspended in a 1:1 mixture of PEG 400 and water, and administered by gavage to fertilized rabbits from day 6 until day 18 of pregnancy, inclusive. The dams were killed, and fetuses removed by Caesarean section on day 29 of pregnancy. During necropsy, dams and fetuses were examined per OECD guidelines.
Species/strain:	Rabbit, chinchilla type
Sex:	20 females/dose group
Route of administration:	Gavage
Duration of the test:	29 Days
Exposure period:	Days 6 to 18 (inclusive)
Frequency of treatment:	Daily
Doses:	0, 200, 600, 1200 mg/kg body weight
Control group:	PEG 400/distilled water, 1:1
GLP:	Yes
Year:	1983
Results:	This chemical was not embryotoxic, and did not produce teratogenic effects under the experimental conditions. There were no significant adverse effect on the dams and their progeny (no significant differences for litter parameters, values for pre-implantation loss, litter size and weight, skeletal anomalies and variants).
Remarks:	This study is assigned a reliability code of 1 (reliable without restrictions) according to the criteria established by Klimisch *et al* (1997).
Reference:	"Report on Irgafos 168 (TK 11 682) teratology study in rabbits." Test No. 82 0874, Ciba-Geigy Ltd., Basel, Switzerland, 1983.

GENERAL REFERENCE

Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology*. 25:1-5, 1997.

Definition of codes

1 = Valid without restriction
1a: GLP guideline study
1b: Comparable to guideline study
1c: Meets national standard methods (AFNOR/DIN)
1d: Meets generally accepted scientific standards and is described in sufficient detail

2 = Valid with restriction
2a: Guideline study without detailed documentation
2b: Guideline study with acceptable restrictions
2c: Comparable to guideline study with acceptable restrictions
2d: Meets national standard methods with acceptable restrictions
2e: Meets generally accepted scientific standards, well documented and acceptable for assessment
2f: Accepted calculation method
2g: Data from Handbook or collection of data

3 = Invalid
3a: Documentation insufficient for assessment
3b: Significant methodological deficiencies
3c: Unsuitable test system

4 = Not assignable
4a: Abstract
4b: Secondary literature
4c: Original reference not yet available
4d: Original reference in foreign language
4e: Documentation in sufficient for assessment